Nitromusks: Human health tier III assessment

8 March 2019

Chemical Name on the Inventory	CAS Number
Ethanone, 1-[4-(1,1-dimethylethyl)-2,6-dimethyl-3,5-dinitrophenyl]-	81-14-1
Benzene, 1-(1,1-dimethylethyl)-3,5-dimethyl-2,4,6-trinitro-	81-15-2
1H-Indene, 2,3-dihydro-1,1,3,3,5-pentamethyl-4,6-dinitro-	116-66-5
Benzene, 1-(1,1-dimethylethyl)-3,4,5-trimethyl-2,6-dinitro-	145-39-1

Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted 4 years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has 3 tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted and published separately, using information available at the time, and may be undertaken at different tiers.

This chemical or group of chemicals is being assessed at Tier III because the Tier II assessment indicated that it needed further investigation. The report should be read in conjunction with the Tier II assessment.

For more detail on this program please visit: www.nicnas.gov.au

Disclaimer

Acronyms & Abbreviations

Synopsis

The nitromusks musk xylene, musk ketone, musk tibetene and musk moskene are synthetic fragrances used in domestic and personal care products. Concerns that repeated exposure to these chemicals could adversely affect human health were raised in the IMAP Tier II assessment. Therefore more detailed quantitative risk assessments were undertaken at the Tier III level.

The quantitative risk assessments were conducted using a margin of exposure (MOE) approach to evaluate the potential health risk associated with exposure to musk xylene and musk ketone used in the cosmetic, personal care and domestic products. The exposure assessment indicated that the chemicals musk moskene and moskene tibetene are not in use overseas and are unlikely to be used in Australia. Therefore, they were not considered in the quantitative risk assessment. The risk assessments indicated that the chemicals pose a low risk to human health. Therefore, no further risk management is required.

The human health Tier II assessment report (NICNASa) for these chemicals is available here and contains detailed assessment information that remains valid. New or updated information is included in the relevant sections of the Tier III Human Health report. The Tier II and Tier III reports for these chemicals should be read together.

Rationale for Tier III Assessment

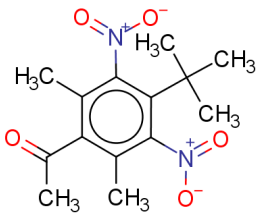
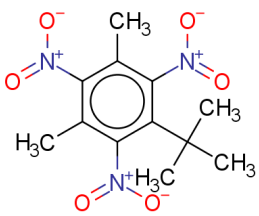
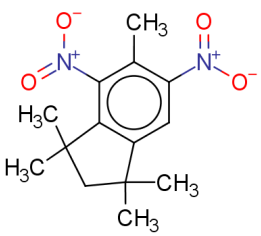
The use of nitromusks is declining and the chemicals are gradually getting replaced by other synthetic musks, including polycyclic and macrocyclic musks (ECHA, 2008). Despite this decline in use, the public may still be exposed to the chemicals through use as fragrances in cosmetics and domestic products including detergents, fabric softeners, household cleaning products and other fragranced products (NICNASa).

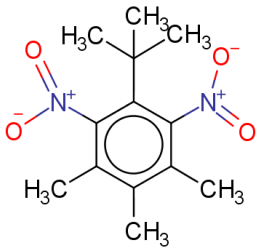
Musk ketone (CAS No. 81-14-1) and musk xylene (CAS No. 81-15-2) are suspected carcinogens (Carc. Cat. 2) (HCIS). The main organ affected by repeated exposures to nitromusks is the liver. The reported adverse effects include changes in liver weight (musk xylene, musk ketone and musk moskene), liver histology (musk xylene and musk ketone) and liver cancer (musk xylene) (ECB, 2005a-b).

Due to a potential public exposure and the hazard profile of the chemicals, a detailed quantitative risk assessment was recommended in the Human Health Hazard IMAP Tier II assessment to determine whether the chemicals pose a risk to public at their current use levels.

Human Health Tier II assessment for the chemical, including information not part of Tier III assessment, is available here.

Chemical Identity

Chemical name on the Inventory and Synonyms	CAS Number	Structural Formula	Molecular Formula	Molecular Weight
Ethanone, 1-[4-(1,1-dimethylethyl)-2,6-dimethyl-3,5-dinitrophenyl]- acetophenone, 4-tert-butyl-2,6-dimethyl-3,5-dinitro musk ketone 2,6-dinitro-3,5-dimethyl-4-acetyl-tert-butylbenzene	81-14-1		C14H18N2O5	294.30
Benzene, 1-(1,1-dimethylethyl)-3,5-dimethyl-2,4,6-trinitro- benzene, 1-tert-butyl-3,5-dimethyl-2,4,6-trinitro musk xylene 5-tert-butyl-2,4,6-trinitro-m-xylene	81-15-2		C12H15N3O6	297.30
1H-Indene, 2,3-dihydro-1,1,3,3,5-pentamethyl-4,6-dinitro- musk moskene 4,6-dinitro-1,1,3,3,5-pentamethylindan moskene	116-66-5		C14H18N2O4	278.31

Chemical name on the Inventory and Synonyms	CAS Number	Structural Formula	Molecular Formula	Molecular Weight
Benzene, 1-(1,1-dimethylethyl)-3,4,5-trimethyl-2,6-dinitro- musk tibetene	145-39-1		C13H18N2O4	266.30

Import, Manufacture and Use

Australian

While no specific Australian use, import, or manufacturing information has been identified, the chemicals were detected in products in both Europe and Asia (Roosens at al., 2007: Lu et al., 2011; Llompart et al., 2013; Nakata et al., 2015). It is likely that a similar range of products is available in Australia.

Musk ketone, musk xylene and musk tibetene may have non-industrial uses as excipients in medicines for topical use only (TGA, 2018).

International

The following use information has been **updated** since the Tier II assessment was published.

In 2018, musk ketone was registered in REACH at the tonnage band 100–1000 tonnes per annum indicating significant use (REACH). In 2016, musk ketone and musk xylene were reported to be present in 17 and 11 preparations, respectively, in Nordic countries (SPIN). A Chinese study published in 2011 found musk ketone to be present in over half of the 158 household products tested, with musk xylene detected in 1 in 5 of the tested products (Lu, et al., 2011). Several companies such as Unilever, Johnson & Johnson and Procter and Gamble reported that they have stopped using nitromusks in their products (Unilever; Johnson & Johnson; and Procter & Gamble).

Cosmetic uses

Musk ketone and musk xylene have reported cosmetic uses as fragrances in personal care products (NICNASa). Musk ketone is the primary nitromusk used in cosmetics (OSPAR, 2004).

Musk ketone is listed in the United States (US) Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary.

The chemicals are not listed in the Compilation of Ingredients Used in Cosmetics in the United States (CIUCUS, 2011).

No cosmetic uses were identified for musk moskene and musk tibetene.

Domestic uses

Musk ketone and musk xylene have reported domestic uses as fragrances in (NICNASa):

- washing and cleaning products; and
- air fresheners.

Musk xylene is expected to be the primary nitromusk in detergents and soaps (OSPAR, 2004). The chemicals are not listed in the US household product database (US HPD).

No domestic uses were identified for musk moskene and musk tibetene.

Restrictions

International

The following information has been **updated** since the Tier II assessment was published.

Musk ketone and musk xylene are restricted in cosmetics in the European Union, New Zealand and Association of Southeast Asian Nations (ASEAN) countries and China (NICNASa).

These restrictions are:

- 1.4 % for musk ketone and 1.0 % for musk xylene in fine fragrance;
- 0.56 % for musk ketone and 0.4 % for musk xylene in eau de toilette; and
- 0.042 % for musk ketone and 0.03 % for musk xylene in other products.

In the EU, musk moskene and musk tibetene are prohibited for use in cosmetics (EC, 2009) and use of musk xylene is prohibited, unless an authorisation is granted (EC, 2009). Musk tibetene is prohibited for use in cosmetic products in Canada (Cosmetic Ingredient Hotlist).

The chemicals, except for musk ketone, are listed as prohibited in the International Fragrance Association (IFRA) Standards (47th amendment). Musk xylene, musk tibetene and musk moskene were not reported by IFRA as being used in fragrance compounds in 2017 (IFRA, 2017). The IFRA standard restricts impurities of musk xylene in musk ketone to 0.1 %. The IFRA-affiliated member companies represent approximately 90 % of the world's production volume of fragrances.

Exposure

Public Exposure

The chemicals are used as fragrances in personal care and domestic products. Available international use information indicates that musk ketone and musk xylene are incorporated in to a wide variety of products. The formulations of similar products on the market in Australia are not assumed to be significantly different from those found internationally. Therefore, musk xylene and musk ketone are expected to be found in a range of personal care and domestic products available for use in Australia.

Musk moskene and musk tibetene are prohibited in many countries and no use was identified for them (see **Use & Restrictions** sections). Therefore, the public exposure assessment will focus on exposure to musk xylene and musk ketone, which are expected to pose the highest risk among this group of chemicals, via cosmetic, personal care and domestic products.

The exposure assessments for cosmetic and personal care products are based on concentrations reported by industry in the 1999 (SCCNFP, 2004) and current restrictions (see ***Restrictions*** section). Exposure from domestic products, including washing powder and air fresheners were based on data provided to European Chemical Bureau (ECB) by industry (ECB, 2005a-b).

Exposure to musk xylene and musk ketone from cosmetic and personal care products

The main route of public exposure to musk ketone and musk xylene is expected to be through dermal contact with cosmetic and personal care products. Part of the applied dose of the chemicals may evaporate and lead to inhalation exposure. However, this part is expected to be very small compared to the dermal exposure due to the low volatility of musk ketone (vapour pressure 0.00004 Pa and Henry's Law coefficient 0.0256 $Pa.m^3/mol$) and musk xylene (vapour pressure 0.00003 Pa and Henry's Law coefficient 0.0595 $Pa.m^3/mol$).

The external dermal exposure doses ($D_{external}$) from cosmetic and personal care products were estimated using Equation 1 (SCCS, 2012).

Equation 1

$$D_{external} = \frac{A_{prod} \times n \times \frac{C}{100} \times RF \times CF}{BW}$$

Where:

$D_{external}$	=	External exposure dose via the dermal route, µg/kg bw/d
A_{prod}	=	Amount of cosmetic/personal care product applied to skin, mg/event
n	=	Frequency of product application, event/d
C	=	Concentration of musk in product, % (w/w)
RF	=	Retention factor
CF	=	Conversion factor, 1000 µg/mg
BW	=	70 kg [lifetime average bw males & females combined (enHealth2012)].

Limited data are available on concentrations of musk xylene and musk ketone in cosmetic and personal care products. Concentrations in cosmetics and personal care products provided by industry in 1999 were in the ranges 0.02–0.6 % and 0.02–0.5 % for musk xylene and musk ketone, respectively (SCCNFP, 2004; Table 1). These were based on the upper 97.5th percentile level of the chemical (fragrance ingredient) in fragrance mixtures containing the chemical. More recent measurements of nitromusk levels demonstrate that the actual concentrations of musk xylene and musk ketone in personal care products are generally below 0.03 % (for details see **Appendix**, Table A1–2). However, these studies are not comprehensive enough to be used for risk assessment. Current restrictions (see **Restrictions**) are also expected to guide and limit the levels of musk xylene and musk ketone in cosmetic and personal care products.

Based on the available concentration information (described above) and the current restrictions, two different exposure scenarios were considered (Table 1):

- the concentrations reported by industry in 1999 (SCCS, 2004); and
- the highest allowable concentrations in EU and several Asian and Oceanian countries (see **Restrictions**).

Table 1 Concentrations of the chemicals present in products used for calculation of dose from dermal exposure ($D_{external}$) from cosmetic and personal care products. Reported concentrations are reproduced from (SCCNFP, 2004). Restrictions are from EC Annex III (EC, 2009). These restrictions have also been adopted in countries outside the EU (see **Restrictions**).

Product	Reported concentrations (%)		Existing restrictions (%)	
	Musk ketone	Musk xylene	Musk ketone	Musk xylene
Body lotion	0.028	0.028	0.042	0.03
Face cream	0.021	0.021	0.042	0.03

Eau de toilette	0.552	0.568	1.4*	1
Fragrance cream	0.276	0.284	0.042	0.03
Antiperspirant/deodorant	0.069	0.071	0.042	0.03
Shampoo	0.035	0.036	0.042	0.03
Bath products	0.138	0.142	0.042	0.03
Shower gel	0.083	0.085	0.042	0.03
Bar soap (Savon de toilette)	0.104	0.107	0.042	0.03
Hairspray	0.035	0.036	0.042	0.03

* Eau de toilettes in this instance includes all hydroalcoholic products (i.e. perfumes, aftershaves, colognes, etc.); therefore the value for fine fragrance is used rather than the lower value that is applicable for eau de toilettes only.

No Australian data on use patterns such as typical amount in each application, frequency of use or exposure duration are available. For the purposes of this assessment, Australian use patterns for the cosmetic and personal care products evaluated in this assessment are considered similar to those in Europe. Consequently, values based on overseas data (SCCNFP, 2004) were used to estimate exposure to musk ketone and musk xylene in Australia (Table 2). The reported concentrations in certain types of products were provided by cosmetic industry and used in a previous European risk assessment of the chemicals in cosmetic and personal care products (SCCNFP, 2004). The EU Scientific Committee on Consumer Safety (SCCS) has recently updated the exposure parameters and the range of products for which they are provided (SCCS, 2018). To match the products for which industry reported concentrations were available, the use related parameters were used as described in SCCNFP, 2004. Using the 2018 exposure parameters, the exposure would be slightly higher but it would not change the outcome of the assessment.

Table 2 Exposure parameters used for calculation of the external dose from dermal exposure ($D_{external}$) to cosmetic and personal care products (SCCNFP, 2004).

Product type	**Aprod – (mg product)**	**n (event/ day)**	**RF**
Body lotion	8000	1.00	1

Product type	Aprod – (mg product)	n (event/ day)	RF
Face cream	800	2.00	1
Eau de toilette	750	1.00	1
Fragrance cream	5000	0	1
Antiperspirant/deodorant	500	1	1
Shampoo	8000	1.00	0.1
Bath products	17,000	0.29	0.01
Shower gel	5000	2	0.1
Bar soap (Savon de toilette)	800	6	0.1
Hairspray	5000	2	0.1

The estimated aggregated exposure doses of musk xylene and musk ketone arising from the combined use of cosmetic and personal care products were calculated based on industry reported concentrations or concentrations based on international restrictions in cosmetic and personal care products (Table 1), and default exposure parameters (Table 2). The dermal exposure doses are summarised in Table 3 (for detailed information, see **Appendix**, Tables A3-A6).

Table 3 The calculated dermal exposure doses ($D_{external}$) for musk xylene and musk ketone from cosmetic and personal care products.

Nitromusk	Reported concentrations* ($D_{external}$, mg/kg bw/day)	Existing restrictions** ($D_{external}$, mg/kg bw/day)
Musk xylene	**0.207**	**0.171**

Nitromusk	Reported concentrations* ($D_{external}$, mg/kg bw/day)	Existing restrictions** ($D_{external}$, mg/kg bw/day)
Musk ketone	**0.187**	**0.239**

*SCCNFP, 2004

**EC Regulation 1223/2009 Annex III

Exposure from domestic products

Exposure to musk xylene and musk ketone from household products was considered negligible compared to exposure from cosmetic products in a risk assessment by the European Chemicals Bureau (ECB, 2005). The exposure was estimated to be approximately 3 % of the exposure from the cosmetic uses. The reported exposure estimates to musk ketone and musk xylene from detergent and air fresheners are summarised in Table 4 (ECB, 2005). Note, the exposure doses from domestic products in Table 4 are shown as µg/kg bw/day compared to mg/kg bw/day for cosmetic and personal care products in Table 3.

Table 4 The reported dermal exposure doses ($D_{external}$) for musk xylene and musk ketone from domestic products (ECB, 2005a-b).

Nitromusk	Detergents (µg/kg bw/day)	Air fresheners (µg/kg bw/day)
Musk xylene	0.26	5.5
Musk ketone	0.25	5.6

Biomonitoring

Musk xylene and musk ketone have been detected in human blood from non-detectable (ND; <4 ng/L) up to 190 and 1520 ng/L for musk xylene and musk ketone, respectively (Government of Canada, 2018; Hutter, 2010). Musk xylene and musk ketone have also been detected in breast milk at concentrations of 150 to 240 ng/g lipid weight and 6.0 to 212 ng/g lipid weight, for musk xylene and musk ketone, respectively (Government of Canada, 2018). The measured concentrations of the chemicals in blood can provide an estimate of integrated exposure for individuals from all routes (oral, dermal and inhalation) and all sources (including environmental media, diet, and frequent or daily use products to which they were exposed) (Government of Canada, 2018).

Health Hazard Information

Toxicokinetics

The following information has been **updated** since the Tier II assessment was published.

In rats, dermal absorption was estimated to be 20 and 40 % for musk xylene and musk ketone, respectively (Table 5). Experimental data suggest that the absorption of musk xylene and musk ketone in humans is lower, approximately 10 and 14 % (Table 5). Pharmacokinetic modelling suggests that absorption of musk xylene in humans may be < 10 % (Government of Canada, 2018).

After oral exposure, approximately 50 % of musk xylene and musk ketone is estimated to be absorbed (ECB, 2005a;b).

There are no data available for toxicokinetics of musk xylene or musk ketone after inhalation exposure.

Table 5 Dermal absorption values taken forward for risk characterisation.

Nitromusk	**Rat**	**Human**
Musk xylene	20 %	10 %
Musk ketone	40 %	14 %

Dermal exposure

In rats, approximately 20 % of the applied dose of ^{14}C-labelled musk xylene was absorbed over 48 h, with the skin acting as a reservoir over the period 6–48 h. Radioactivity was detected in most tissues with peak concentrations after 8 h. Excretion was predominantly via bile and was virtually complete within 48 h.

In humans musk xylene was poorly absorbed with < 1 % of the applied dose excreted within 120 h. Plasma peak levels of musk xylene were also low (0.03–0.06 % of the applied dose) (ECB, 2005b). Approximately 90 % of the applied dose was recovered from the application site. The dermal absorption was, therefore, conservatively assigned to be 10 % which corresponds to 20 % of the estimated oral bioavailability (50%) in humans (see **Toxicokinetics – Oral exposure**). In a recent pharmacokinetic two-compartment modelling study based on toxicokinetic data from rats and humans (cited in Government of Canada, 2018), dermal bioavailability was estimated to be significantly less (2 % of the oral bioavailability). This was consistent with the relative systemic bioavailability (oral/dermal) based on plasma levels of musk xylene estimated by Riedel and Dekant, 1999 (cited in ECB, 2005b). Therefore, in vivo dermal absorption in humans is likely to be < 10 % (Government of Canada, 2018).

In rats approximately 40 % of the applied dose of musk ketone was absorbed within 48 h of dermal application. Radioactivity was detected in most tissues with peak concentrations found after 6 h. Excretion occurred mainly via bile over 5 days with most of the radioactivity eliminated during the first 48 h (ECB, 2005a).

Musk ketone is poorly absorbed from human skin. Only 0.5 % of the applied radiolabelled musk ketone was recovered from urine and faeces of human volunteers. However, 14 % of the dose was unaccounted for. Therefore, as a conservative approach, dermal absorption of musk ketone was estimated to be 14 % (ECB, 2005a; NICNASa).

Oral exposure

Insufficient information is available to estimate oral bioavailability of musk xylene. Plasma peak levels of musk xylene in humans indicated low oral absorption (0.6–3.8 %) but this is considered an underestimate since a significant amount of musk xylene is distributed to adipose tissue and other organs (ECB, 2005; NICNASa). In rats, oral absorption of 12 % was derived based on the amount excreted in urine and carcass; this value is also considered an underestimate as it does not account for biliary excretion (ECB, 2005b). Using the biliary excretion from dermal studies, assuming that contribution of biliary excretion to the total excretion is equal after oral and dermal absorption, the oral absorption in rats and humans was estimated to be approximately 50 % (ECB, 2005b; NICNASa).

There are no data available on the toxicokinetics of musk ketone after oral exposure. However, based on similar physico-chemical properties and similar dermal uptake, the oral absorption is assumed to be similar to musk xylene.

Repeated Dose Toxicity

The following information has been **updated** since the Tier II assessment was published.

The studies used to derive the no-observed-adverse-effect-level (NOAEL) and supporting oral studies are summarised below. Further details of these studies can be found in the Human Health Tier II assessment of nitromusks (NICNASa). The main route of exposure to nitromusks is dermal (see **Exposure assessment**). Therefore, the NOAEL for risk assessment was based on a well-performed 90-day dermal repeated dose toxicity study. Oral toxicity studies were also considered as supporting evidence; however, the information available from these studies was not sufficient for derivation of an NOAEL.

Based on the 90-day dermal study and supporting oral studies, the target organ for musk xylene and musk ketone is the liver. Liver weight increases were observed in the 90-day dermal study in rats for both musk ketone and musk xylene (Table 6), as well as in oral studies in mice and rats (ECB, 2005 a-b; NICNASa). Effects on liver histology were only observed at high oral doses in mice. Liver damage was reported in a 1-year oral study in rats with musk ketone (not included in the Tier II assessment). In this study, rats received musk ketone at 50, 125 or 500 mg/kg bw/day for 1 year. Effects observed at the 2 highest doses included slight thyroid hyperplasia and fatty vacuolisation of pancreatic acinar cells. Liver damage, slight anaemia, cellular atrophy of the testes, increased blood cell production and osteoporosis were observed at the high dose only. A NOAEL of 50 mg/kg bw/day was reported (USA FDA, 1969). No further details are available for the study.

Table 6 Lowest observed adverse effect levels (LOAEL) values and no observed adverse effect level (NOAEL) values (mg/kg bw/day) derived from the dermal 90-day repeated dose toxicity study in male (M) and female (F) mice.

Nitromusk	Sex	LOAEL (mg/kg bw/day)	Absolute liver weight (% increase from control)	Relative liver weight (% increase from control)	NOAEL (mg/kg bw/day)
musk ketone	M	NA	NS	NS	240
	F	240	20 %	50 %	75
musk xylene	M	240	16 %	13 %	75
	F	75	15 %	12 %	24

NA = Not available.

NS = Non-significant.

Carcinogenicity

The following information has been **updated** since the Tier II assessment was published.

The chemicals, musk ketone and musk xylene, are classified as hazardous— Carcinogenicity – Category 2—with the risk phrase 'H351 (Suspected of causing cancer)' in the HCIS (Safe Work Australia).

Based on currently available data (NICNASa), it is difficult to determine the carcinogenic potential of musk xylene and musk ketone. This is because:

- only 1 species (mouse) has been tested;
- the tested mouse strain (B6C3F1) is particularly prone to tumour development;
- the suggested mechanisms may not be relevant for humans; and
- carcinogenicity data for musk ketone and related nitromusks (musk moskene and musk tibetene) are limited or absent and not able to support the carcinogenicity classification.

In an 80 day study in B6C3F1 mice exposed to musk xylene via the diet, incidences of hepatocellular adenomas and carcinomas were significantly increased in both males and females when compared to controls. However, histologically, the majority of the adenomas and carcinomas were similar to those tumours found in control mice. The mouse strain (B6C3F1) used in this study is particularly prone to development of liver tumours. The historical incidences of spontaneous tumours in control animals were in the ranges 10–68 % in males and 6–56 % in females (Haseman, 1998). The tumour incidences reported in control and musk xylene treated mice were within this range. Therefore, without testing the musk xylene in another species (or another strain of mouse), it is difficult to determine the carcinogenic potential of musk xylene. An LOAEL of 70 mg/kg bw/day for musk xylene was deduced from the study (Maekawa et al., 1990; ECB, 2005a-b).

The chemicals are proposed to have a non-genotoxic mechanism of carcinogenicity similar to that for phenobarbital (Lehman-McKeeman et al., 1997). However, the relevance of the proposed non-genotoxic mechanism of carcinogenicity in humans has been questioned (Elcombe et al., 2014).

Data on carcinogenicity for musk ketone are limited. Liver injury, but no adenoma or carcinoma was reported in a 1-year oral chronic study in rats treated with musk ketone (see **Repeated dose toxicity** section).

Selection of NOAEL for risk characterisation

The most relevant route of exposure to nitromusks is via the dermal route. Information available from oral studies is not sufficient for derivation of a NOAEL. The carcinogenic potential of musk xylene and musk ketone is not well established, although any mechanism of carcinogenicity is assumed to be non-genotoxic. A NOAEL has not been established in carcinogenicity studies.

The NOAEL values for risk assessment are selected based on 90-day dermal repeated dose toxicity studies (see ***Repeated dose toxicity*** section***)***. The selected NOAEL values are 24 mg/kg bw/day for musk xylene and 75 mg/kg bw/day for musk ketone based on changes in liver weights (Table 6). Liver hypertrophy in response to enzyme induction is generally considered adaptive and of little relevance to humans. However, exposure levels that have previously led to adaptation may eventually, if adaptation fails, lead to liver injury (Hall, 2012). In the 90-day dermal repeated dose toxicity study, there was no evidence of liver injury or histological changes in the liver. Therefore, the change in liver weight can be considered a very conservative NOAEL for the risk assessment.

Risk Characterisation

Public Risk Characterisation

A MOE methodology was used to characterise the risk to human health associated with the exposure to musk xylene and musk ketone. This was approach was considered acceptable due to the non-genotoxic mechanism of toxicity (see **Health Hazard Assessment**). A MOE methodology is commonly used to characterise risks to human health associated with exposure to chemicals (ECB, 2003). The risk characterisation is conducted by comparing quantitative exposure information with a NOAEL selected from appropriate animal studies and deriving an MOE as follows:

1. Identification of critical health effect(s).

2. Identification of the most appropriate/reliable NOAEL for the critical health effect(s).

3. Comparison of the estimated or measured human dose or exposure (EHD) with the appropriate/reliable NOAEL to provide an MOE:

$$MOE = NOAEL/EHD$$

4. Evaluation as to whether the MOE obtained by this method indicates a health concern for the human population under consideration.

The MOE risk estimate provides a measure of the likelihood that a particular adverse health effect will occur under the conditions of exposure. As the MOE increases, the risk of potential adverse effects decreases. To decide whether the MOE is of sufficient magnitude, expert judgment is required. Such judgments are usually made on a case-by-case basis, and should take into account uncertainties arising in the risk assessment process such as the completeness and quality of available data, the nature and severity of effect(s) and intra/inter species variability. With the interspecies and intraspecies assessment factors of 10, the acceptable MOE for NOAEL-based assessment is 100 or greater.

Risk estimates related to use of cosmetic and personal care products

The main route of exposure to musk ketone and musk xylene is through dermal contact with cosmetic or personal care products. Inhalation exposure is considered negligible due to the low vapour pressure of the chemicals.

The starting points for risk characterisation are external exposure levels ($D_{external}$; Table 3) estimated based on reported concentrations and restrictions (Table 1). The NOAEL values for musk xylene and musk ketone for risk characterisation are derived from a 90-day dermal repeated dose toxicity study in rats (see **Repeated dose toxicity** section). The MOE methodology was used for characterising the public health risks from musk xylene and musk ketone exposure through simultaneous use of cosmetic and personal care products (Tables 7 & 8). The NOAEL values were adjusted for differences in absorption between humans and rats (Table 5).

The estimated external exposure levels based on reported concentrations and restrictions for musk xylene were 0.207 and 0.171 mg/kg bw/day, respectively (Table 3). The NOAEL for risk characterisation for musk xylene is 24 mg/kg bw/day (Table 6). Adjusting for the difference between rat dermal absorption (20 %) and human dermal absorption (10 %) gives an adjusted NOAEL of 48 mg/kg bw/day (Table 7).

The estimated external exposure levels based on reported concentrations and restrictions for musk ketone were 0.187 and 0.239 mg/kg bw/day, respectively (Table 3). The NOAEL for risk characterisation for musk ketone is 75 mg/kg bw/day (Table 6). Adjusting for the difference between rat dermal absorption (40 %) and human dermal absorption (14 %) gives an adjusted NOAEL of 214 mg/kg bw/day (Table 8).

The MOE values for the critical health effects of musk xylene and musk ketone were calculated based on estimated aggregate exposure in the general population accounting for species differences in absorption (Table 7 & 8).

Table 7 Calculated MOE for the critical health effect of musk xylene from estimated aggregate exposure to cosmetic products for the general population

Concentration of musk xylene (%)	Adjusted $NOAEL_{derm}$ (mg/kg bw/day)	Dermal Exposure dose (mg/kg bw/day)	MOE
Reported concentrations (0.021-0.552)	48	0.207	232
Existing restrictions (0.03-1)	48	0.171	281

Table 8 Calculated MOE for the critical health effect of musk ketone from estimated aggregate exposure to cosmetic products for the general population

Concentration of musk ketone (%)	Adjusted $NOAEL_{derm}$ (mg/kg bw/day)	Dermal Exposure dose (mg/kg bw/day)	MOE
Reported concentrations (0.021-0.552)	214	0.187	1144
Existing restrictions (0.042-1.4)	214	0.239	895

The estimated MOEs for musk ketone and musk xylene were all well above 100 for the potential exposure scenarios. This indicates that the risk of liver toxicity in the general population from use of multiple cosmetic products is low.

This risk estimate can be considered very conservative for a number of reasons. Firstly, the estimates of consumer exposure to musk xylene and musk ketone are based on the 97.5th percentile level of the fragrance ingredients. It is unlikely that a consumer will consistently use a range of different products all perfumed with the same fragrance ingredient in the upper 97.5th percentile. Furthermore, recent measurements of actual concentrations in products in Asian and European countries are substantially lower than the reported or restricted concentrations used in the exposure assessment (Table A1–2). Secondly, absorption in humans is likely to be lower than the 10 % and 14 % used in the estimate of internal exposure (see **Toxicokinetics** section). Thirdly, the NOAEL values for risk assessment were based on increases in liver weights in a 90-day dermal repeated dose toxicity study. This selection of the NOAEL could be considered very conservative since it is based on an effect that is generally considered adaptive rather than adverse. Finally, while the chemicals are classified as suspected carcinogens based on a study in mice, the evidence supporting this classification is weak (see **Carcinogenicity** section). Despite the conservative approaches used in the assessment, the MOE analysis above suggests that it is unlikely that musk xylene or musk ketone will have adverse effects on the liver at the current exposure levels.

Risk estimates related to use of domestic products containing musk ketone or musk xylene

Exposure to musk xylene and musk ketone from household products was considered negligible compared to exposure from cosmetic products; therefore, no further risk management is required.

Risk estimates based on biomonitoring

Human biomonitoring data are important for risk assessment where internal concentrations may increase over time from regular exposure. Musk xylene and musk ketone are both lipophilic with slow elimination; therefore, cumulative effects are of concern.

Musk xylene and musk ketone have been detected in human blood at 190 and 760 ng/L (~0.190 and 0.760 µg/kg), respectively. In rats exposed to musk xylene or musk ketone at a concentration (0.5 mg/kg bw/day) much lower than the NOAEL (75 or 24 mg/kg bw/day) for 14 days, the blood levels were 116 µg/kg for musk xylene and 240 µg/kg for musk ketone (Hawkins et al., 1999). The concentrations of the chemicals detected in blood in rats at doses significantly below the NOAEL (2 % or less of the NOAEL) were at least 315 times higher than the blood levels observed in humans. These findings further support the conclusion that the human exposure to the chemicals is not expected to pose a risk.

Conclusions

The MOEs for musk xylene and musk ketone are well above 100 and, therefore, considered acceptable for a risk assessment based on an NOAEL. Together with the conservative approaches taken in both the risk and the hazard assessments, musk xylene and musk ketone are not considered to pose an unreasonable risk to public health. No national or international uses were identified for musk moskene and musk tibetene (see **Use** section).

This assessment has also demonstrated that the current levels of musk xylene and musk ketone reported in the scientific literature are substantially lower than the reported and the restricted concentrations used in the MOE calculations.

Finally, the uses of nitromusks have declined in the last decade and several companies have declared that they have stopped using the chemicals (Johnson and Johnson; Unilever; and Procter & Gamble). Environmental assessments of chemicals in this group have determined that musk xylene is persistent, bioaccumulative and toxic (PBT) to the environment and musk ketone is persistent and toxic (NICNASb). Therefore, environmental regulations are also expected to limit the use of the chemicals, further supporting the conservatism of the exposure assessment.

Considering the low risk of toxicity from use of the chemicals in cosmetic, personal care or domestic products and the expected decline in use, no further risk management is required.

NICNAS Recommendation

Current risk management measures are considered adequate to protect public and workers' health and safety, provided that all requirements are met under workplace health and safety, and poisons legislation as adopted by the relevant state or territory. No further assessment is required.

The advice provided for worker health and safety in the Human Health Tier II IMAP report remains unchanged.

Advice for consumers

Products containing the chemical should be used according to instructions on the label.

Advice for industry

The advice provided in the Human Health Tier II IMAP report remains unchanged.

A review of the physical hazards of the chemical has not been undertaken as part of this assessment.

Appendix

Table A1 Measured concentrations of musk ketone in personal care products 2007–2015.

Concentration (%, w/w)	Product type	Country	Reference
0.001	Baby shampoo	Portugal	Homem, 2015
0.001	Body soap	Japan	Nakata, 2015
0.00005	Body wash	China	Lu, 2011
0.0000057	Deodorant	Belgium	Roosens, 2007

Concentration (%, w/w)	Product type	Country	Reference
0.002	Gel soap	Portugal	Homem, 2015
0.0000157	Hair care	Belgium	Roosens, 2007
0.008	Hair care	China	Lu, 2011
0.0001	Hair conditioner	Portugal	Homem, 2015
0.0006	Hair gel	Spain	Llompart, 2013
0.002	Hand cream	Portugal	Homem, 2015
< 0.0000003	Lotion	Belgium	Roosens, 2007
0.0001	Make-up	China	Lu, 2011
< 0.0000003	Perfume	Belgium	Roosens, 2007
0.02	Perfume	Japan	Nakata, 2015
0.0000013	Sanitation	Belgium	Roosens, 2007
< 0.0000003	Shower product	Belgium	Roosens, 2007
0.005	Skin lotion	China	Lu, 2011
0.001	Skin lotion	China	Lu, 2011

Table A2 Measured concentrations of musk xylene in personal care products 2007–2015.

Concentration (%, w/w)	Product type	Country	Reference
0.0003	Baby shampoo	Portugal	Homem, 2015
0.000003	Body milk	Spain	Llompart, 2013
0.0000001	Body wash	China	Lu, 2011
0.000008	Deodorant	Belgium	Roosens, 2007
0.0000044	Hair care	Belgium	Roosens, 2007
0.000041	Hair care	China	Lu, 2011
0.03	Hair nutrition	Spain	Llompart, 2013
0.00002	Hair nutrition	Spain	Llompart, 2013
0.001	Lotions	Belgium	Roosens, 2007
< 0.0000003	Perfume	Belgium	Roosens, 2007
0.000004	Sanitation	Belgium	Roosens, 2007
0.000003	Shower product	Belgium	Roosens, 2007
0.001	Skin lotion	China	Lu, 2011

Table A3 Total exposure dose of musk ketone from personal care products based on concentrations reported by industry in 1999 (SCCS, 2004).

Product type	$C_{reported}$ (%)	Bw	D_{derm} mg/kg bw/day
Body lotion	0.028	70	0.032
Face cream	0.021	70	0.005
Eau de toilette	0.552	70	0.059
Fragrance cream	0.276	70	0.057
Antiperspirant/deodorant	0.069	70	0.005
Shampoo	0.035	70	0.004
Bath products	0.138	70	0.001
Shower gel	0.083	70	0.012
Bar soap (Savon de toilette)	0.104	70	0.007
Hairspray	0.035	70	0.005
		Total	**0.187**

Table A4 Total exposure dose of musk xylene from personal care products based on concentrations reported by industry.

Product type	$C_{reported}$ (%)	Bw	D_{derm} mg/kg bw/day
Body lotion	0.028	70	0.0320

Product type	$C_{reported}$ (%)	Bw	D_{derm} mg/kg bw/day
Face cream	0.021	70	0.0048
Eau de toilette	0.568	70	0.0609
Fragrance cream	0.284	70	0.0588
Antiperspirant/deodorant	0.071	70	0.0051
Shampoo	0.036	70	0.0041
Bath products	0.142	70	0.0003
Shower gel	0.085	70	0.0203
Bar soap (Savon de toilette)	0.107	70	0.0058
Hairspray	0.036	70	0.0153
		Total	**0.207**

Table A5 Total exposure dose of musk ketone from personal care products based on restrictions.

Product type	$C_{restricted}$ (%)	Bw	D_{derm} mg/kg bw/day
Body lotion	0.042	70	0.0480
Face cream	0.042	70	0.0096

Product type	$C_{restricted}$ (%)	Bw		D_{derm} mg/kg bw/day
Eau de toilette	1.4	70		0.1500
Fragrance cream	0.042	70		0.0087
Antiperspirant/deodorant	0.042	70		0.0030
Shampoo	0.042	70		0.0048
Bath products	0.042	70		0.0003
Shower gel	0.042	70		0.0060
Bar soap (Savon de toilette)	0.042	70		0.0029
Hairspray	0.042	70		0.0060
			Total	**0.239**

Table A6 Total exposure dose from personal care products based on restrictions.

Product type	$C_{restricted}$ (%)	Bw	D_{derm} mg/kg bw/day
Body lotion	0.03	70	0.0343
Face cream	0.03	70	0.0069
Eau de toilette	1	70	0.1071

Product type	$C_{restricted}$ (%)	Bw	D_{derm} mg/kg bw/day
Fragrance cream	0.03	70	0.0062
Antiperspirant/deodorant	0.03	70	0.0021
Shampoo	0.03	70	0.0034
Bath products	0.03	70	0.0002
Shower gel	0.03	70	0.0043
Bar soap (Savon de toilette)	0.03	70	0.0021
Hairspray	0.03	70	0.0043
		Total	**0.171**

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